

# Biosimilars: Still Not Quite Ready for Prime Time

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## Basics About Biosimilars and the Marketplace

The United States is the largest biologics market in the world and has the highest prices for biologics, which include monoclonal antibodies, therapeutic proteins, immunomodulators, and growth factors. Unlike traditional chemical drugs, most biologics are not distributed via traditional distribution channels but instead are considered “specialty”

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drugs, which are supplied via specialty pharmacy distribution services. Biologics and so-called specialty pharmaceuticals represent the highest growth rate pharmaceutical sector in the U.S., outpacing overall performance of the pharmaceutical market.

The rapidly expanding biologics segment is projected to account for about 20% of the global drug market by 2017.<sup>1</sup> Today, many of the top health care expenditure drugs are biologics, e.g., infliximab (Remicade, Janssen), rituximab (Rituxan, Genentech, Inc./Biogen Idec Inc.), bevacizumab (Avastin, Genentech, Inc.), trastuzumab (Herceptin, Genentech, Inc.), and epoetin alfa (Epogen, Amgen; Procrit, Janssen). Despite this, biologics continue to be a less accessible, more expensive treatment option for patients and a drain for commercial insurance, Medicare, Medicaid, and self-insured employers.

While this is not news to managed care plans, hospitals, or health systems, the status of alternatives to brand biologic and specialty drugs remains nebulous and confusing to many. Other than knowing that biosimilars represent a potential savings opportunity, how and when that can happen remain unclear. This article explores the legal and regulatory facts

around biosimilars to date, with application to the U.S. marketplace.

## Legal and Regulatory Foundation

The Biologics Price Competition and Innovation (BPCI) Act, a statutory provision of the Patient Protection and Affordable Care Act (PPACA) of 2010, creates an abbreviated Biologic License Application (aBLA) pathway for licensure of biosimilar products under §351(k) of the Public Health Service Act.<sup>2</sup> To facilitate the process, which the Food and Drug Administration (FDA) refers to as a “totality of the evidence” approach, it issued various guidance documents, which are summarized in Table 1.<sup>3-6</sup> These guidances establish the core regulatory framework for U.S. biosimilars. In the guidance pertaining to biosimilar naming, the FDA has proposed to require a unique four-letter suffix so that the biosimilar can be distinguished from the reference drug to allow for traceability and to prevent “inadvertent substitution.” The latest guidance pertains to labeling. In that guidance, the FDA recommends that biosimilar labeling incorporate data from the reference product labeling with appropriate product-specific modifications. The guidance also provides spe-

**Table 1 FDA Guidance Documents<sup>3-6</sup>**

Biosimilars: Q&A	Naming Conventions	Scientific Considerations	Quality Considerations	Labeling
<ul style="list-style-type: none"> <li>Marketing exclusivity</li> <li>Amount/number of reserve samples</li> <li>Publicly available information</li> <li>Interchangeability</li> <li>Same dosage form defined</li> <li>Pediatric information</li> <li>IND</li> </ul>	<ul style="list-style-type: none"> <li>Four-letter suffix</li> <li>Share nonproprietary name</li> </ul>	<ul style="list-style-type: none"> <li>Totality of the evidence</li> <li>Stepwise approach</li> <li>Post-marketing surveillance</li> <li>Clinical data extrapolation</li> <li>Analytical, PK, PD</li> <li>Comparison studies</li> <li>Immunogenicity</li> </ul>	<ul style="list-style-type: none"> <li>Receptor binding</li> <li>Impurities</li> <li>Immunogenicity</li> <li>Stability</li> <li>CMC data submission</li> <li>Reference product</li> <li>Finished product</li> <li>Application of ICH guidelines</li> </ul>	<ul style="list-style-type: none"> <li>Incorporate relevant reference product labeling information</li> <li>Include product-specific modifications (e.g., storage)</li> <li>Biosimilarity statement</li> <li>Immunogenicity statement</li> <li>Product identification approach (core versus reference names)</li> </ul>

CMC = chemistry, manufacturing, and controls; ICH = International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; IND = investigational new drug; PD = pharmacodynamics; PK = pharmacokinetics.

Table 2 Glossary

- **Biosimilar**—A biological product, notwithstanding minor differences in clinically inactive components, that is “highly similar” to the reference product and for which there are no clinically meaningful differences from the approved biological product in terms of safety, purity, and potency.
- **Reference drug**—Biologic product that is FDA approved prior to submission of an aBLA.
- **aBLA**—Abbreviated Biologic License Application
- **Interchangeable biosimilar**—Requirements for interchangeability are: 1) the biosimilar can be expected to produce the same clinical result as the reference product in any given patient, and 2) for products that are administered more than once to the patient, switching between reference drug and biosimilar products is safe and efficacious.
- **Follow-on biologic**—Earlier preferred term for biosimilars in the U.S. Biosimilars, biobetters, and biogenerics are all follow-on biologics.
- **Biological product**—A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product applicable to the prevention, treatment, or cure of a disease or condition in human beings.
- **Biobetter**—Newer versions of marketed biotherapeutic agents engineered for improved properties.
- **Biogeneric**—An interchangeable biosimilar.
- **Extrapolation**—The process of granting a clinical indication to a medication without its own or new clinical safety and efficacy studies to support that indication.

cific labeling wording for statements regarding biosimilarity and immunogenicity.<sup>6</sup> The FDA intends to publish guidances for interchangeability and statistical evaluations to support a demonstration of biosimilarity. The 351(k) process is clearly evolving, and the need for clinical trials will be evaluated on a case-by-case basis.<sup>7</sup>

The BPCI Act sets forth definitions, basic requirements, and patent litigation processes. A glossary of terms is found in Table 2. Biosimilar means that the biological product is highly similar to the reference product even if there are minor

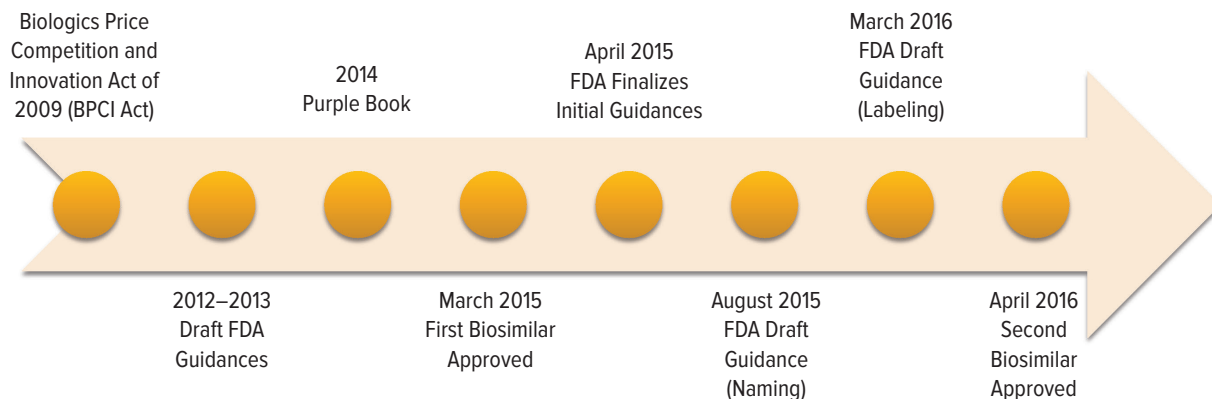
differences in clinically inactive components, and there are no clinically meaningful differences between the biosimilar and the reference product in terms of the safety, purity, and potency. However, not all biosimilars are interchangeable. Interchangeable means that the biological is biosimilar to the reference product; can be expected to produce the same clinical result as the reference product in any given patient; and for a product administered more than once, the safety and reduced efficacy risks of alternating or switching between the reference product and the biosimilar are not greater

than with repeated use of the reference product. Inasmuch as the FDA is still considering what information is needed for demonstrating interchangeability, no biosimilar has applied for status as an interchangeable biosimilar.

In 2005, the European Medicines Agency became the first regulatory body to establish an approval process and guidelines for biosimilars, and multiple biosimilars are marketed in Europe.<sup>8</sup> Biosimilars also exist in Japan, Canada, India, China, Australia, Latin America, and other countries, although of varying quality, safety, and efficacy. In May 2015, the first biosimilar, filgrastim-sndz (Zarxio, Sandoz, Inc.), was approved in the U.S. by the FDA, although litigation delayed marketing until September 2015.<sup>9</sup> In April 2016, the second biosimilar, infliximab-dyyb (Inflectra, Celltrion/Pfizer) was FDA approved. A biosimilar timeline is detailed in Figure 1. Additional biosimilar applications for adalimumab (Humira, AbbVie, Inc.), etanercept (Embrex, Amgen), pegfilgrastim (Neulasta, Amgen), and epoetin alfa (Epogen, Amgen; Procrit, Janssen) have recently been submitted to the FDA.

Market introduction of biosimilar products represents hope for patients with debilitating and life-threatening diseases and a cost savings for the health care system. Cost savings estimates for biosimilars range from \$25 billion to \$44 billion over 10 years, depending on the source.<sup>10,11</sup>

Figure 1 Biosimilar Timeline



**Table 3 Similarities and Differences Between Biosimilars and Reference Biologic Products**

Similarities	Differences
<ul style="list-style-type: none"> <li>Exact same primary structure</li> <li>Indications (but biosimilar may be approved for fewer indications than the reference product)</li> <li>Labeling</li> <li>Strength and dose</li> <li>Route of administration (but biosimilar may be approved for fewer routes than the reference product)</li> <li>No clinically meaningful difference in biologic activity</li> <li>Bioequivalency</li> <li>Purity, safety, and potency</li> <li>Mechanism of action</li> </ul>	<ul style="list-style-type: none"> <li>Minor structural variations (e.g., glycosylation patterns, amino acid sequence)</li> <li>Costs</li> <li>Packaging and delivery systems</li> <li>Inactive components/formulation</li> <li>Stability/storage requirements/expiration dating</li> <li>No biogenerics. Only “interchangeable” upon FDA determination</li> <li>Manufacturing processes (e.g., cell lines, cell culture, purification)</li> <li>Naming conventions (e.g., suffix)</li> <li>Exclusivity: 12 years for reference drug; none for biosimilar</li> </ul>

**Table 4 Comparison of Biosimilars and Generic Drugs**

Generic Drugs	Biosimilars
<ul style="list-style-type: none"> <li>Approved for all indications</li> <li>ANDA for approval</li> <li>No disease state trials required for approval</li> <li>Orange Book governs substitution</li> <li>Identical copies can be made</li> <li>Chemical, low-weight molecules; stable</li> <li>Hatch-Waxman patent litigation process</li> <li>180-day exclusivity for first generic ANDA approved</li> <li>Lower research and development costs</li> </ul>	<ul style="list-style-type: none"> <li>Extrapolation of indications possible</li> <li>351(k) for approval</li> <li>Clinical trials required</li> <li>Purple Book governs substitution</li> <li>Impossible to fully characterize molecular composition (even reference biologics have some lot-to-lot variability)</li> <li>Protein, large molecules, produced in living systems; unstable</li> <li>BPCI Act “patent dance” litigation process</li> <li>One-year exclusivity for first interchangeable biosimilar approved under a 351(k); no exclusivity for first noninterchangeable biosimilar</li> <li>Higher research and development costs</li> </ul>

ANDA = abbreviated new drug application; BPCI = Biologics Price Competition and Innovation.

### Know the Details: Safety And Efficacy Compared With Reference Biologics

Under §351 (k), a manufacturer seeking to market a biosimilar must submit an aBLA with scientific data demonstrating, among other things, that the biological product has the same mechanism(s) of action, safety, purity, potency, and bioequivalency and no clinically meaningful difference in biologic activity. A comparison of biosimilars and reference biologic products is found in Table 3. One significant difference is that a biosimilar may not be required to provide full product-specific nonclinical and clinical data to be

licensed. Instead, it may rely upon certain existing scientific knowledge about the safety, purity, and potency of the reference product. Clinical studies for all uses are not mandated if the biosimilar and reference drug share the same mechanism of action. Extrapolation of indications by the FDA is permitted.

Interchangeability under the BPCI Act is a higher standard than biosimilarity, and clinical switching studies are required to support this determination. The FDA has stated it will not make determinations of interchangeability for new biosimilars.

### Interchangeability Is Important To Know for Biologics

#### Biosimilar Interchangeability Does Not Equal Generic Substitution

In several European countries, automated substitution of biosimilars is prohibited by legal/regulatory measures. Unlike generic drugs, biosimilars cannot be assumed to be interchangeable with the reference product, nor can two different biosimilars of the same reference product be considered equivalent. A comparison of biosimilars and generic drugs is found in Table 4. Switching between reference biologic drug and biosimilar is currently regarded as a change in clinical management unless the two are deemed “interchangeable.” Under the BPCI Act, interchangeable biosimilars may be substituted for the reference product without intervention of the prescribing health care provider.

Analogizing the BPCI Act with the Hatch-Waxman Act, like the Orange Book for generic drugs, the FDA has created the Purple Book, also known as “Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations.” Interchangeable biosimilars will eventually be listed in the Purple Book.

The FDA determines interchangeability but state boards of pharmacy, not the FDA, control automatic substitution. Despite the fact that the FDA determines interchangeability, has not done so yet, and has stated that it will not do so right now, and even before the FDA finished defining its aBLA process, biosimilar substitution bills were introduced in at least 32 states and were signed into law in 17 states plus Puerto Rico.<sup>12</sup> The patchwork of existing and proposed state laws contains provisions that range from prescriber veto power and prior notification to automatic substitution based upon an FDA interchangeability determination. In states with mandatory generic drug substitution (e.g., New York), biosimilar substitution laws do not invalidate those laws. Typical features of the state substitution laws are presented in Table 5.<sup>13</sup> Because only biosimilars deemed “interchangeable” by the FDA would be substitutable by a pharmacist without the intervention of a prescriber, and because the FDA has not even determined what the requirements for that determination would be, it would seem that enactment of the laws is

**Table 5 Provisions of Various State Laws and Legislation Pertaining to Biosimilars**

- Food and Drug Administration must designate “interchangeable”
- Prescriber preference (may write “dispense as written” or “brand medically necessary”)
- Prescriber notification if substitution occurs
- Patient notification if substitution occurs
- Patient consent for substitution
- Retention of records by prescriber
- Retention of records by pharmacist
- State must maintain a public or Web-based list of permissible interchangeable products
- Pharmacist must explain the cost or price of the biologic and the interchangeable biosimilar
- Immunity for pharmacists who make a substitution in accordance with state law

premature. That is, noninterchangeable biosimilars could never be substituted for each other. Even interchangeable biosimilars could not be substituted for each other. An interchangeability determination only applies to a specific biosimilar and the reference product, and does not apply between or among multiple biosimilars approved to a single reference product. Additionally, multiple biosimilars to a reference drug may not share all indications.

Despite this, various professional and patient organizations and health care stakeholders have already aligned themselves either for or against automatic biosimilar substitution (Figure 2). Supporters believe the state proposals are restrictive, are inconsistent with the federal approach, and will increase health care costs. Opponents believe the ulti-

mate decision should be left up to the prescriber and/or patient.

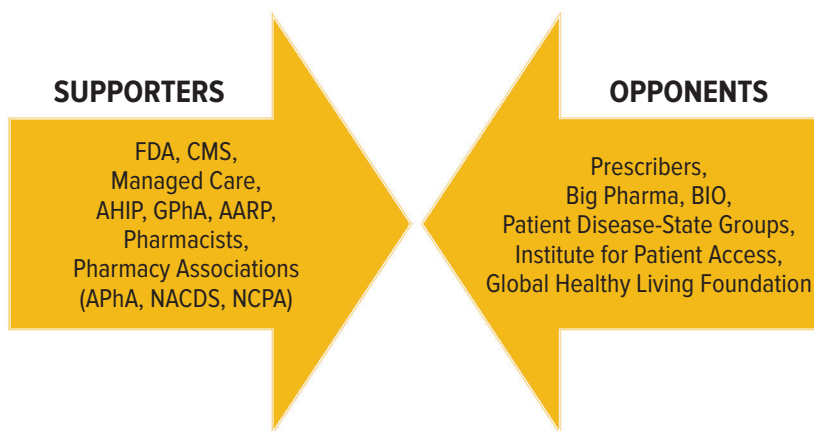
### Patents, Positioning, and Reimbursement Models

It is estimated that it will cost approximately \$100 million to \$200 million to develop a biosimilar versus the \$800 million it costs to develop an innovator biologic<sup>14</sup> versus the \$1 million to \$4 million for developing a generic drug. Developing a biosimilar requires a seven- to eight-year investment in time with only a 50/50 probability of success.<sup>15</sup> Additional barriers to U.S. biosimilar adoption are found in Table 6. Patent litigation represents yet another potential challenge for the market entry of biosimilars. Manufacturers are required to create biosimilars without infringing on any manufacturing patents of the reference product. The

patent litigation process of the BPCI Act is commonly referred to as “the patent dance.”<sup>16</sup> A number of lawsuits are currently pending between reference manufacturers and biosimilar applicants involving conflicting interpretation of the “patent dance” process.<sup>17–19</sup> How these cases are decided will set the stage for implementation of the BPCI Act for years to come.

Reference drug manufacturers are not just waiting idly for the onslaught of biosimilars to erode their market share. Some are improving their products. For example, for MabThera (rituximab, Roche), the reference company designed a formulation to cut treatment time from 2.5 hours to minutes. For epoetin, which requires multiple weekly doses, the second-generation product requires only weekly injections. Others are filing Citizen Petitions for various reasons in an effort to delay biosimilar entry. One Citizen Petition, for example, requests that biosimilars be labeled to clearly identify the indications for which they are approved. Right now it appears that labeling will follow the style for generic drugs, which are labeled almost identically to the brand drugs. However, according to the FDA’s recent labeling guidance, biosimilar labeling should be specific to the approved indications for the biosimilar products. The biosimilar labeling could also include differences in administration, preparation, storage, or safety information. All of these barriers and factors will affect costs and, consequently, payer and reimbursement models.

Off-label use will be an issue for biosimilars that are not designated interchangeable by the FDA. If interchangeable, the biosimilar will be approved for all the indications of the reference drug. But what happens when the biosimilar is not an interchangeable biosimilar and, therefore, not listed in the Purple Book? How does the prescriber: 1) know a biosimilar version is available, and 2) know what indications that biosimilar has been approved for in relation to the reference drug? For example, the FDA approved filgrastim-sndz, the first biosimilar, for all the indications of the reference product filgrastim (Neupogen, Amgen). However, the reference drug manufacturer subsequently received approval for an additional indication. Consequently, the biosimilar and reference product are not approved for the same indications.

**Figure 2 Automatic Substitution**

AHIP = America's Health Insurance Plans; APhA = American Pharmacists Association; BIO = Biotechnology Innovation Organization; CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; GPhA = Generic Pharmaceutical Association; NACDS = National Association of Chain Drug Stores; NCPA = National Community Pharmacists Association.



**Table 6 Barriers Impeding U.S. Biosimilar Adoption**

- Onerous 351(k) interchangeability requirements
- Costs associated with biosimilar development
- Unclear requirements for clinical data
- Patent litigation delaying biosimilar entrants
- Public disclosure of proprietary data
- Naming conventions with different nonproprietary names
- New formulations
- Patchwork of individual state substitution laws
- Patient and/or prescriber caution
- Payer reimbursement uncertainties

Once a biosimilar obtains FDA approval, the next challenge is for the manufacturer to market the product at a lower cost than the reference product. In Europe, where biosimilar prices are approximately 15% to 30% below the reference product, market uptake for biosimilars has been slow.<sup>20</sup> For example, market penetration of biosimilar epoetin ranges from 3.2% in the United Kingdom to 26.3% in Germany.<sup>21</sup>

Likely biosimilars, with their abbreviated approval process, will be priced 20% to 40% less than reference products. As such, it will still be cost-effective for reference manufacturers to remain in the market. Of course, some reference drug manufacturers may choose not to compete, leaving the biosimilars without competition—much like the generic drug situation, where the prices of generics have increased as a result. An alternative scenario is that biosimilars may drive down the price of the reference drug, which will occur as more biosimilars are introduced.<sup>22</sup>

Insufficient price discounts coupled with prescriber, pharmacist, and/or payer reluctance to substitute for the reference drug may result in a vastly different brand erosion dynamic for interchangeable biologics than has been seen historically with generic drugs. These factors have prompted some to speculate that, for biologics, the loss of revenue will be about 30% over five years compared to the 90% revenue loss with generic drugs for the same period.<sup>23</sup> Many believe that payers will treat biosimilars like lower-cost

brand products rather than like generics.

Costs will be a key determinant of biosimilar acceptance. Reimbursement, patient assistance programs, copays, and formulary status for biosimilars will vary by payer, and many payers are restructuring benefit design and meeting with external partners to discuss biosimilars. Additionally, new payment system changes, such as accountable care organizations (ACOs) bundled payments, where lump sum amounts are provided to cover a given episode of care, and value-based measures will drive use of lower-cost biosimilars.<sup>24</sup> Most payer groups, such as Veterans Affairs, pharmacy benefit managers (PBMs), ACOs, managed care organizations, and integrated delivery networks, are making biosimilar planning a priority.<sup>25</sup> Employers are excited about potential cost savings and are awaiting input from both their health plans and PBMs.

Health insurance providers are eager to find ways to combat the rising cost of prescription drugs, and biosimilars may find success through favorable treatment by third-party payers. Insurers may choose to reduce patient cost sharing for biosimilars altogether to incentivize patients to switch from the reference drug. Insurers may take reference biologics off their formularies altogether and replace them with biosimilars. Maybe switching will be required for new or treatment-naïve patients only. Which of these scenarios will occur remains to be determined.

Many biologics are injected or infused, often in specialist physician offices, hospitals, or clinics. Unlike oral therapies, which are managed by payers as drug benefits, biosimilars and reference drugs are managed by payers as medical benefits. This also has implications for market entry for biosimilars.

Formulary review in outpatient settings differs greatly from inpatient review. On the outpatient side, PBMs will likely review each biosimilar individually and use patient financial incentives to drive their use (e.g., implementing a 20% copay for a fourth-tier biologic versus a third-tier biosimilar). A recent health plan study revealed that half of them plan to place biosimilars on a lower cost share tier than reference drugs.<sup>26</sup>

The Centers for Medicare and Medicaid Services (CMS) has issued several guidelines on biosimilar reimburse-

ment. Under Medicare Part B, CMS will reimburse biosimilars at the average sales price plus 6% of the average sales price of the reference drug in order to reduce incentives for prescribing the more expensive reference drug. Using this model for payment, Medicare will save \$4 billion over a 10-year period.<sup>27</sup> Biosimilars will share the same Healthcare Common Procedure Coding System code (i.e., J code). Under this model, all biosimilars for a reference product will be priced the same. Medicaid will most likely adopt biosimilars over higher-priced reference drugs. Medicare Part D vendors may institute specialty tiers in their formularies for reference drugs and biosimilars. However, there are CMS-imposed limitations on what Part D vendors may do with respect to the specialty tier. For Medicaid, biosimilars will be considered “single-source drugs” under the rebate program, which means biosimilar manufacturers will pay rebates on state Medicaid utilization based on the formula for branded drugs, not generics.

The recent trend has been to place high-priced biologics into the specialty pharmacy distribution model. However, in view of the expected competition, distribution models are likely to be unrestricted rather than resembling those of specialty drugs. A distinct marketing advantage will be achieved if the biosimilar is unrestricted while the reference product is limited to the specialty pharmacy distribution model.<sup>28</sup>

Stakeholders making formulary decisions are also going to be looking at the quality and services of the biosimilar manufacturer, such as patient assistance programs, copay foundations, patient compliance services, and ease of access (e.g., preauthorization). Pharmacy access is a significant factor for biosimilar acceptance. Generic drugs gained market share with automatic substitution at the pharmacy level. Without automatic substitution, manufacturers must compete like a branded drug and will have to invest substantial resources to market a biosimilar to prescribers and health systems, such as hospitals.

## Medical and Pharmacy Practice Implications

Biosimilars have profound implications for formulary management and control down to the patient level. Change and

**Table 7 Pharmacy Practice Implications**

- Opportunities and responsibilities
- Awareness of federal/state substitution requirements
- Pharmacovigilance
- Education
- Medication reconciliation
- Transitions of care
- Inventory management

implications on pharmacy practice are already acute (Table 7). At the micro-level, pharmacists should be prepared to lead the evaluation of comparability regarding manufacturing differences, pharmacokinetics, immunogenicity, storage, indications, and interchangeability in collaboration with other stakeholders in health care.

### Education

Patients are likely to have many questions for both prescribers and pharmacists regarding the efficacy and safety of biosimilars. While patient education will be needed, the questions with regard to the myriad of state substitution laws are: What is the pharmacist required to notify the patient about, and what is the patient consenting to? It is disturbing to these authors that only one state biosimilar substitution law requires patient education, that is, patient counseling, on the use and expected response.

Pharmacists, prescribers, and patients overall will need more education about biosimilars. Some research indicates that few clinicians have come to a conclusion about the use of biosimilars in their practice. A recent survey of oncologists suggests that they are unfamiliar with issues surrounding biosimilar medications.<sup>29</sup> Just as some prescribers never embraced generics, lack of education will result in segments of prescribers who will not prescribe biosimilars. Biosimilars represent an opportunity for pharmacists to advise other clinicians and patients, empowering them to make informed decisions.

### Pharmacovigilance

Robust pharmacovigilance requirements as a component of a risk management system are important for biosimilars where clinical trials may have been performed in smaller numbers of

patients, resulting in a smaller safety database. Pharmacists are well positioned to monitor and identify biosimilar safety issues, such as possible immunogenicity, or other adverse effects, such as potential infections.

Concerns have also been raised for extrapolation of indications, where, for example, a biosimilar that was studied in one tumor type may also be approved for use in another tumor type without new clinical data.<sup>30</sup>

Another concern is that repetitive switching between different biosimilars and a reference drug will lead to immunogenicity. An analogy is the use of generic immunosuppressants in transplant patients. However, this concern would appear moot, as a biosimilar will be found interchangeable with a reference drug, not with another biosimilar. So once a patient is switched from a reference product to a biosimilar, the patient would not be able to be switched to another interchangeable biosimilar. For traceability, health systems may resort to online logs, similar to what is required for albumin and other blood-type products.

Since 2012, a European Union directive requires all biosimilars to be identified with a symbol to indicate they are subject to additional post-marketing safety monitoring.<sup>31</sup> Unfortunately, there are inadequacies in current U.S. adverse drug reaction (ADR) reporting systems, where ADR reporting is voluntary for prescribers and underreporting is prevalent. Thus, notification of biosimilar substitution by pharmacists to prescribers may not be effective. As the FDA considers naming and traceability, perhaps it should consider changes to its current ADR reporting requirements to proactively address concerns about accurate tracking.<sup>32</sup>

### Community-Based Pharmacy

Right now, without interchangeability, switching a patient from a reference drug to a biosimilar would require a new prescription or at least a telephone call for an oral prescription. With generics, the substitution is clear. Past practice with state substitution laws is that they emphasize the pharmacist's professional responsibility for determining, on the basis of available evidence, that the drug products they dispense are equivalents. Not so with biosimilars. However, in a recent survey,

75% of pharmacists were confident or very confident with interchangeability if the biosimilar and reference drug share the same nonproprietary name.<sup>33</sup>

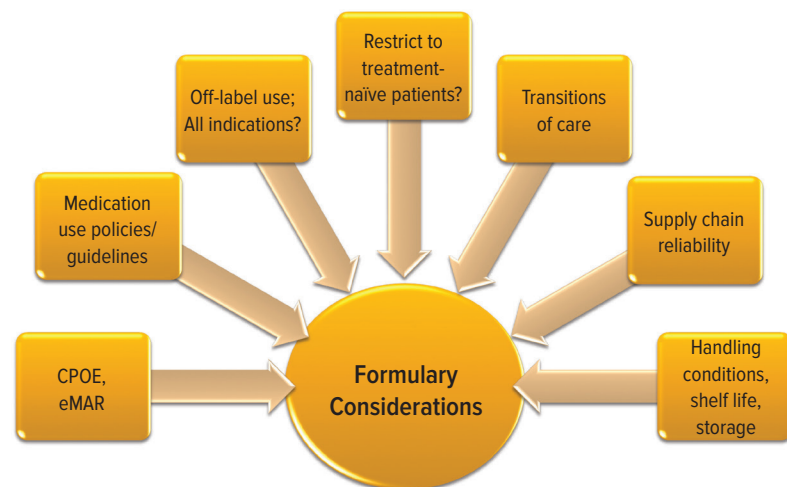
There are unsettled questions about whether patients and prescribers should be notified of a biosimilar substitution and how. Provisions of the various state legislation pertaining to biosimilar substitution include three main provisions: 1) notification of prescriber and/or patient if substitution occurs (some states require the pharmacist to explain the cost/price of the biologic and the interchangeable biosimilar; notification ranges from 24 hours to "reasonable time" to 10 days, depending on the state), 2) prescriber prohibition (may write "dispense as written" or "brand medically necessary"), and 3) patient refusal or consent for substitution.<sup>27</sup>

Notification ultimately serves to discourage pharmacist substitution. Studies have shown that brand drug usage increased by 29% when physician notification was required.<sup>34</sup> The restrictions imposed on substitution are yet another barrier to U.S. market entry of biosimilars. Interchangeable biologic substitution processes that require authorization, recordkeeping, or reporting beyond generic product substitution processes may prove unnecessarily restrictive to substitution and unnecessarily burdensome to pharmacists. Pharmacists will need to be aware of their state's law, which could limit their ability to switch patients to interchangeable biosimilars.

Inventory management issues may occur. With generics, pharmacies need only stock one generic version to fill all prescriptions. However, for biosimilars, pharmacies will have a difficult time stocking all variants of a biosimilar.

How will prescribers know that a biosimilar version of a reference drug is available? How will they know the biosimilar is approved for all indications? Pharmacists are familiar with the Orange Book and will be familiar with the Purple Book. Prescribers are unlikely to use the Purple Book, and do not have time to go into that level of detail. Prescribers rely on pharmacists for generic substitution, and the process is transparent. Transparency in labeling and reliance on pharmacists as experts in biosimilar products will facilitate biosimilar adoption.

Under the current provisions of many

**Figure 3 Formulary Considerations for Biosimilars**

CPOE = computerized provider order entry; eMAR = electronic medication administration records.

state biosimilar substitution laws, the process is cumbersome. Even if the prescriber is notified of the biosimilar dispensed, as mentioned above, ADR reporting is not mandatory for prescribers.

### Health System Pharmacy

A number of factors will impact P&T committee decisions concerning use of biosimilars in hospitals and health systems (Figure 3). P&T decision-makers will be looking at the efficacy of biosimilars; interchangeability; product and administration issues, such as dosage form, routes of administration, storage requirements, stability, supply chain availability, history of recalls, market penetration, packaging and labeling, delivery system, and practitioner preferences; and cost and reimbursement.<sup>35</sup> The stakes are high as hospital systems continue to move toward single, system-wide formularies.

Hospitals will be applying principles of therapeutic substitution or therapeutic interchange to biosimilars. An important issue is whether the biosimilar with limited approved indications will be added to formularies only for those indications or whether they be used off-label as well. Obviously, the more reference product indications the biosimilar has obtained, the more likely it is to be substituted. However, what happens when the off-label use is the standard of care and the health system is currently using the reference drug off-label? Will payers reim-

burse for off-label use? It will be necessary to decide whether the biosimilar can be extrapolated to off-label indications for which the reference drug is used but not FDA approved. That is, hospitals will need to conduct their own extrapolation assessment of off-label indications, especially for oncology medications. In the future, compendia and organizations may develop guidelines to assist with these decisions.<sup>36</sup> Otherwise, hospitals will need to carry both the reference product and the biosimilar, which will affect cost savings. Any determinations of interchangeability will also be of great import in determining whether the biosimilar is a formulary addition or a formulary replacement for the reference drug.

Changes will be needed for information systems, such as pharmacy dispensing systems, order sets, computerized provider order entry, and electronic medication administration records, as well as policies and guidelines. Inventory systems (e.g., bar-coding) will also need to be revised. In institutions where the reference drug is included on many protocols, the staff hours needed to change those systems may offset any cost savings. The biosimilar may not be priced favorably enough to undertake these extensive changes.

When patients transition from the community to the hospital and then from the hospital back to the community, there is a potential for switching patients to different biosimilars, as well as a potential

for errors. Some hospitals might be able to purchase reference biologics under favorable 340B pricing or via bundling with other products, where the biosimilar may not be the least expensive product in all circumstances. However, rebates or discounts may be available from both the reference or biosimilar manufacturers. The hospital is faced with the issue of whether to forgo these discounts to minimize switching patients at discharge (i.e., transitions of care) where the patient is discharged with a prescription for a less expensive biosimilar version.<sup>37</sup> When the biosimilar is dispensed from the health system's inpatient pharmacy, which product is on formulary will depend on whether the hospital will be responsible for absorbing the costs in the long run (e.g., patients without a payer source).

Policies will need to be developed on a product-by-product basis for these transitions-of-care scenarios.

### Biosimilar Acceptability to Patients and Providers Remains Unknown

Acceptability to patients and prescribers is a big unknown, as both are poised to challenge payers and PBMs who may more readily adopt biosimilars on economics alone. Prescribers see biosimilars as additional work. They may need to review clinical data, check the FDA Purple Book, discuss substitution with the pharmacist, and explain the switch to their patients. The question is: Will insurers mandate the switch? Will switching harm the patient who was doing well on the reference product? The American College of Rheumatology has issued a position statement that says no switching by an insurer, pharmacist, or third party for any reason that is not a medical one should be permitted. In a recent survey of 300 primary care and specialist physicians, 94% believed biosimilars will add value to health care, but only 17% stated they would be very likely to prescribe them. The main concerns were safety issues, such as possible immunogenicity; efficacy; substitution regulations; and accurate evaluation of when to prescribe them versus a reference drug.

Like brand drug companies that often now make their own generics, biosimilar applications are likely to come from both companies that are focused on biosimilars as well as reference drug companies



looking to pursue biosimilars of their competitor's innovative products. Those companies that focus solely on reference products will, similar to some brand drug manufacturers, attempt to promote the concept of biosimilar product inferiority. They may encourage clinicians to believe that biosimilar product variations could be clinically significant. Clearly, tier assignment for the reference drug and biosimilar will impact their uptake and market share.

There are also risk aversion, status-quo bias, and malpractice concerns given the unknown toxicity of biosimilars. This is reinforced by financial considerations if payment to prescribers is a fixed percentage of the price of the medication as in Medicare Part B. Traceability may help, as ADRs with an untraceable product could have a chilling effect on the entire market.

## Conclusion

Despite approval of the BPCI Act, the intent of which was cost savings in response to ballooning biologic prices, no biosimilar applications were filed with the FDA in the first four years after enactment. Because the process is just now beginning to be used by companies, many questions are unanswered. The FDA is contemplating scientific/technical requirements for interchangeability, ADR tracking, and naming. Much of the unknown comes back to the FDA, its review process, and how much risk prescribers are willing to accept, and how much autonomy will be given to pharmacists. In addition, what actions will P&T committees take within their organizations, and how will that effect utilization management toward enhanced clinical outcomes and improved financial performance for their organization?

Since the arrival of biologic products before 2000 and early product innovations allowing for biologic-based alternatives since 2000, only now are we entering into the biosimilars era. The oncology, gastroenterology, and rheumatology fields are likely to be impacted the most now, as many biosimilars will be in these practice areas.

Medication cost-containment pressures are driving the demand for and interest in having biosimilars available in the U.S. If biosimilars are priced lower than reference biologics, and if safety and

efficacy are not an issue, there will be considerable pressure to utilize biosimilars to control health care costs. More of the health care budget will be available to purchase medications for more patients to use. However, the costs of biosimilars may increase due to a number of factors, such as costs of studies for approval, patent litigation, and a more protracted erosion of reference product market share. That erosion of economic value will likely gate the development and availability of many biosimilars into the market. In the U.S., state substitution laws will impact cost savings and create additional barriers to market entry.

For benefit plan decision-makers and P&T committees today, biosimilars remain more of a promise than an opportunity from a legal perspective. The FDA has yet to truly establish the envisioned pathway that would open up clear development and market availability for biosimilars. Despite press to the contrary, biosimilars remain a realistically unavailable market alternative and a continuing dream to counter the fiscal reality of adopting new technologies such as biologics in a post-PPACA marketplace.

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